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Subject: Depakote in agitation assoc with dementia (LTC)
Date: Mon Jul 07 2003 19:48:54 EDT
Attachments: Depakote in Agitation (Long Term Care-- Summary).doc

REDACTED put together this brief summary of Abbott sponsored and Abbott supported studies in long term care.

----- Forwarded by REDACTED LAKE/PPRD/ABBOTT on 07/07/2003 06:47 PM -----

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07/07/2003 04:40 PM

To REDACTED LAKE/PPRD/ABBOTT@ABBOTT
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Subject: Depakote in agitation assoc with dementia (LTC)

REDACTED

In helping towards PEC prep, I am attaching the summary of Depakote studies with respect to use in agitation associated with dementia.

Basically includes anything that Abbott sponsored or provided funding for that has been "significant" one way or the other.

As you can see from the results of some of these studies, the track record in this area is not great. That is why I was surprised to see it listed as a "candidate" for that meeting.

Hope it helps

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Summary of Abbott-sponsored or funded Key Studies with Depakote in Long Term Care

Abbott Study M96-491

--A Double-Blind, Placebo Controlled Study of Depakote in the Treatment of Behavioral Agitation Associated with Dementia

Three center study, 15 patients, 3 weeks

Depakote DR, 6 in treatment group, 9 in placebo group

Depakote DR started at 125mg BID, titrated by 125mg increments every 1 to 3 days to clinical response, max dose 30mg/kg/day

Range 500mg to 1500mg day for Depakote DR group

Small number of subjects so not powered to show statistical significance, however Depakote DR treated patients demonstrated greater mean decreases (improvement) at each evaluation in the total BEHAVE-AD, YMRS, CGI and OAS

Rochester study (supported by Abbott funding)

-- Placebo-Controlled Study of Divalproex Sodium for Agitation in Dementia (published Am J Psychiatry 2001, Porsteinsson and Tariot)

Study duration was 6 weeks, n=56, avg. dose = 826mg/day, mean VPA level = 45.4

Key results; 68% of Depakote patients showed reduced agitation on the CGI versus 52% placebo (p=0.06)

This was an investigator trial that was supported by funding from Abbott

-- Open Valproate Treatment Following a Double-Blind Trial for Agitation (poster presented at The 8th (2002) International Conference on Alzheimer's Disease and Related Disorders in Stockholm, Abstract 440, Porsteinsson and Tariot)

45 of the 56 patients in the above Rochester study completed a 6-week open extension (mean dose was 851 mg/day)

**Key results; 86% of subjects showed improvement on the CGI (p < 0.001)
Subjects showed a decreased mean BPRS, and BPRS agitation factor (p < 0.002 for both)**

Abbott Study M97-738 (published in Current Therapeutic Research, Jan 2001, Tariot and Schneider

-- A Randomized, Double Blind, Placebo Controlled Multicenter Study Looking at Safety and Efficacy of Depakote in Reducing Signs and Symptoms of Mania Associated with Dementia in Elderly Nursing Home Patients

6 week trial, 172 subjects, 87 Depakote group, 85 in placebo group

Depakote DR titrated in 125 increments every day until 20mg/kg/day

No improvements in mania scale (Bech-Rafaelsen Mania Scale), MMSE or BPRS

CMAI scores showed significant improvement in comparison to placebo

Common adverse effects --somnolence and thrombocytopenia

Study stopped on recommendation of DSMB on 3/12/99 because of higher rate of AE's and reductions in albumin and cholesterol thought to possibly reflect decreased nutrition in Depakote group.

Critiques of the study:

- 1) Depakote was dosed much too aggressively, titration was too rapid for this elderly population, and led to the significant tolerability issues in the trial and it's premature stoppage by the Data Safety Monitoring Board.
- 1) Primary efficacy measure, in retrospect, was a poor choice, since a mania rating scale (Bech-Rafaelsen) was used to evaluate behavior disturbance in an elderly population with dementia. These patients were not bipolar, and likely not experiencing true "mania", but rather the disinhibited behavioral problems seen in such nursing home patients with dementia.

Abbott Study M98-817

--An Open-Label, Non-Comparative, Multicenter Extension of Study M97-738

93 patients enrolled, 12 week safety study

Results similar to M97-738; somnolence was the most common adverse event. The majority of patients who discontinued for adverse events reached doses over 21mg/kg/day

Lead to notion that doses up to 15mg/kg/day (approximately 1000mg/day) should be well tolerated and avoid somnolence and difficulty maintaining adequate oral intake.

Abbott Study M99-082

--A Double Blind, Placebo Controlled Study of Depakote in the Treatment of Behavioral Agitation in Elderly Patients with Dementia

Phase III, original target of 390 patients

Three arms; Compared Placebo to 500mg, and 1000mg of Depakote DR

Company decision to stop at 121 patients due to poor enrollment

Primary efficacy parameter: CMAI

Secondary: CGI, BPRS

Findings showed better safety profile than M97-738 due to slower, more cautious titration, however efficacy data was not impressive for Depakote.

In fact, the placebo group was numerically superior to both Depakote groups, and statistically more efficacious than the Depakote 500mg group. Interpretation of the data was hampered due to the low power of the study (study was powered at 390 patients, and only 121 were randomized).

Enrollment was very slow and main reason cited for prematurely stopping this trial

Critiques of the study:

- 1) 500mg dose group was unlikely to show efficacy over placebo as this final dose is probably too low for most patients to experience any medication benefit.
- 2) Because of all the safety concerns stemming from M97-738, the inclusion/exclusion criteria were seen as overly "stringent" by many, and not reflective of the elderly nursing home population with dementia, thus making enrollment very challenging
- 3) Also due to the previous safety concerns in M97-738, patients received more interpersonal attention from the staff in this trial and it is felt this may have contributed to the very large placebo response.

NIA funded studies (through ADCS--Alzheimer's Disease Cooperative Study)

--- A Randomized, Double Blind, Placebo Controlled Trial to Evaluate the Safety and Efficacy of Divalproex Sodium Therapy for Agitation in Nursing Home Residents with

Dementia

Phase II trial , 6 weeks, patients in NH's with MMSE between 4 - 24

Target of 150 patients ; 75 subjects receiving placebo versus 75 subjects treated with a fixed dose of 750mg of Depakote sprinkle capsules

Enrollment has been completed, but detailed data not seen by Abbott. Dr. Tariot's verbal report of the preliminary findings suggest no evidence of a meaningful treatment difference between the Depakote and placebo groups.

Abbott provided drug, and supplemental funding

Primary efficacy parameter; BPRS
Secondary: ADCS clinical Global Impression of change (CGIC) modified,
focus on agitation
CMAI
MMSE
PSMS (Physical Self Maintenance Scale)

Director; Pierre Tariot, MD, NIA/ADCS Study 012

---ADCS Project 6 -- A Clinical Trial of Valproate to Attenuate the Progression of AD

Double blind, placebo controlled, 2 year study of 300 Alzheimer's patients with mild to moderate dementia (MMSE 10-20).

Looking at outpatients (not NH residents) who have no baseline behavioral disturbance. Want to assess if Depakote treatment leads to delay of the emergence of behavioral disturbance and if it delays course of cognitive decline.

Biological markers are being taken (b-catenin and Bcl-2) to correlate with neuroprotective properties.

Dose of Depakote ER to be determined

Abbott is providing medication, as well as supplemental funding for neuroimaging studies and genomic/proteomics. The National Institute on Aging (NIA) is funding the large majority of this trial.

Study would help establish efficacy and safety of chronic Depakote therapy in this elderly population Also, it could establish Depakote as a drug beneficial for neuroprotection and delay of onset of behavioral disturbances associated with Alzheimer's dementia

Project Director – Pierre Tariot, MD